time period set in the attached Office communication per 37 CFR § 1.85(a) or else the application will become abandoned.

Applicants originally filed formal drawings and our records do not indicate that the PTO has issued any statement regarding the condition of the drawings or a need for any corrections thereon. Further, there is no indication in the February office letter that any corrections are due. Therefore, for purposes of this response, Applicants have assumed that the attachment was meant as a general notice on new procedures rather than a rejection of the existing drawings. Applicants request, however, that the Examiner specifically state for the record whether or not the PTO has made a determination that drawing corrections are necessary as Applicants desire to avoid automatic abandonment of the application if corrections are indeed required.

3. Applicants response letters dated June 28, 2001 and August 8, 2001 requested correction of the specification and provided remarks thereto. However, in the February 14, 2002 office letter the Examiner did not comment upon whether the amendments have been entered. Applicants respectfully request that such amendments be acted upon and entered into the specification. Applicants respectfully further request that the Examiner acknowledge entrance of such amendments.

4. Applicants request the entrance into the record of amended claims 162, 163, 167, 168, 176 and new claims 381 and 382. Given the cancellation of claims 1-161, and their prior replacement by claims 262-380, claims 162, 163, 167 and 168 must be amended with respect to the number of the claims referenced therein. Claim 176 is amended to properly refer to elements commencing with (a)-(d) rather than (e)-(h). A clean copy of the claims and a copy showing the amendments are provided below.

5. Restriction Requirement

The Examiner has required restriction of the invention under 35 U.S.C. § 121. The Examiner found 51 inventions which he divided into 51 groups. Applicants hereby provisionally elect the inventions of Group 15, represented by claims 220-228, with traverse.

As an alternative restriction of claims, Applicants request that the Examiner, in view of Applicant's traversal described below, reformulate the restriction into the following groups, in

which case Applicants provisionally elect the invention of Group I/II, with traverse. Applicants submit that examination of the claims according to the groupings formulated below will drastically simplify the Examiner's approach to examination of this application.

This election of claims is made without prejudice to future prosecution, and does not constitute an admission that any of the non-elected subject matter is un-patentable. Applicant reserves the right to prosecute claims to such subject matter in any appropriate application. Applicants propose grouping of the claims for examination purposes as follows:

Group I - Claims 220-367 drawn to aAPC compositions comprising various elements, (Class 435, subclass 325);

Group II - Claims 368-380 drawn to process of making aAPC, (Class 435, subclass 325);

Group III - Claims: 197-214 and 381, 215 and 382, drawn to kits and apparatuses for using aAPC, (Class 435, subclasses 283.1 and 810);

Group IV - Claims drawn to methods of using aAPC:

- claim 162 drawn to identifying T cells using aAPC, (Class 435, subclass 7.1);
- claims 163-167 drawn to isolating T cells using aAPC, (Class 435, subclass 7.1 and Class 424, subclasses 278.1, 534);
- claims 168-175 drawn to modulating T cell response using aAPC, (Class 424, subclasses 278.1 and 534);
- claims 176-185 drawn to characterizing T cell functional state using aAPC isolated by the method of claim 163, (Class 435, subclass 6);
- claims 186-188, 189-194 drawn to treating a condition using aAPC isolated by the method of claim 163, (Class 424, subclasses 278.1 and 534);
- claim 195 drawn to identifying epitope specific T cells using the method of claim 162, (Class 435, subclass 7.1);
- claim 196 drawn to treating to reduce allograft rejection using the method of claim 162, (Class 424, subclass 184.1);
- claim 218 drawn to obtaining monoclonal T cell population using the method of claim 163, (Class 435, subclasses 7.1, 325);

Group V - Claims 216-217 drawn to method of identifying a gene, (Class 435, subclass 6); and

Group VI - claim 219, drawn to method of monitoring immunological outcome (Class 435, subclass 7.1).

Applicants traversal is based on their proposition that:

(1) the aAPC compositions are directed to a single invention. As stated in the specification at page 10:

> We have discovered a platform technology for advancing treatment regimens requiring the immunoregulation of immune cells that centers around the use of an artificial antigen presenting cell (APC). This platform technology may be designed or programmed on demand for use in the treatment of a broad spectrum of specific disease states. Moreover, this system is versatile and applicable to all situations where the isolation, identification, and modulation of T cells is of clinical import. We have recognized the relevance of several types of molecular entities to the stimulation/activation and modulation response of T cells in their role within the immune system and have incorporated these entities into artificial APCs. We use such artificial APCs to capture and manipulate antigen specific T cells.

At page 13 the specification states:

> The concept of the current invention represents a substantial and heretofore unrecognized advance in the MHC:antigen complex T cell binding art in that the artificial APC (*e.g.* the example comprising liposome:MHC:antigen:accessory molecule:functional molecule complex) is not restricted to complexes of MHC:antigen alone or to a planar surface as is the case with much of the prior art. The importance of the structural differences can not be over emphasized. The addition of the accessory molecules, as well as co-stimulatory molecules, and other proteins in proper orientation in the liposomes of the current invention allow for substantially improved binding association and manipulation of T cells which is very important in the identification and stimulation of antigen-specific T cells. This is especially true in solution based FACS analysis where functionality of the antigen-specific T cells can be interpreted directly.

Further, at page 14 the specification states:

> The current invention's use of co-stimulatory, adhesion and other accessory molecules in a "free floating" format also helps to both anchor and direct the interaction between MHC:antigen:accessory molecule and T cell receptors by providing a means by which T cells in the sample will be presented with a structure more similar to that found in the natural state. Specifically, the MHC:antigen:accessory molecule complexes in conjunction with other functional molecules are able to migrate in proper orientation in the lipid bilayer of the liposome because of the use of a unique combination of lipids and surfactant molecules, namely an optimal ratio of phosphotidylcholine and cholesterol respectively, included in the liposome matrix. These provide particular protein presentation characteristics and easy protein migration properties to the surface of the liposome structure so that the MHC:antigen complexes can easily migrate to T cell

> binding loci similar to "capping" events seen in natural APCs. Moreover, as shown in the figures, the structure of our artificial APC liposomes allows for specific "capping" of the liposomes on the surface of the T cells to which the liposomes are bound. Additionally, interaction between the T cell and artificial APC-associated molecules is further enhanced by the molecules being oriented in the lipid membrane such that their active sites are positioned facing outward on the APC. Without such orientation, the ratio of properly oriented molecules to improperly oriented molecules is around 50:50. This ratio is greatly increased using MHC, functional and accessory proteins that have attached thereto (either by fusion protein construction or by use of a linker) a cholera β toxin subunit moiety which is placed in relation to the active center of the protein of interest such that upon the β subunit being bound by GM-1 which is incorporated into the lipid layer of the artificial APC, the protein of interest will lay in the APC with the active site facing outward.
> Additional versatility is available with the current invention in that the artificial APCs may incorporate irrelevant molecules to be used in conjunction with separate solid support-based capture moieties for capturing generic target motifs such as irrelevant molecules. Because of the capacity for the functional molecules to migrate in the liposome, the irrelevant molecules may be nonspecifically directed away from the binding position of the T cells thus avoiding steric hindrances.

Also, at page 20:

> In one aspect, artificial APCs are provided having a synthetic membrane-based vesicle, such as a liposome containing cholesterol and neutral phopholipids such as phosphotidylcholine, that functions as an APC having capacities equivalent to a natural APC to bind to and induce an antigen-specific T cell response. Such an artificial APC comprises multiples of homo- or heterogenous combinations of MHC:antigen complexes incorporated therein as well as other functional molecules including accessory molecules, co-stimulation molecules, adhesion molecules, and other immunomodulatory molecules such as cytokines, cytokine receptors, chemokines, and chemokine receptors. Additionally, these APCs may include a mechanism to properly orient these molecules of interest in the APC membrane.

As the above excerpts disclose, the invention is directed to aAPC comprising various embodiments. These various embodiments are not independent as they are connected in design and operation and effect as discussed below.

(2) The aAPC comprise combination and subcombinations that are not distinct and fall within a single class and subclass and are related by the elements of the subcombinations as discussed below.

(3) The aAPC and their method of making and method of use are not distinct but in fact linked to one another as there is no material distinction between them as assessed according to criteria laid out in the MPEP as discussed below.

5.1 In response to the office letter dated October 22, 2001, Applicants mailed a paper dated October 30, 2001 electing for prosecution Group I out of Groups I-XIII. Notwithstanding Applicant's election, the Examiner reconsidered the grouping of the claims (ostensibly based on Applicant's canceling of claims 1-161 and submission of new claims 220-380) and multiplied the number of Groups for restriction to 51 Groups. Applicants note that the new claims were essentially identical to the cancelled claims except that in each of the independent claims one element (the same for each claim) was moved from dependent claims and added to the independent claims.

Applicants traverse the restriction and request reconsideration and withdrawal or modification of the requirement under 37 C.F.R. § 1.143 for the reasons set forth below. Further, Applicants Petition the Commissioner to review the requirement under 37 C.F.R. § 1.144. Arguments discussing the errors of the restriction in support of Applicant's Petition are distinctly and specifically set out below with respect to certain of the claims (MPEP 818.03(c). Moreover, due to the nature of the claims comprising related product and process claims, in the event that restriction is held final, Applicants reserve the right to have process of making and process of using claims rejoined with the present application when product claims are found allowable (MPEP 821.04) and 37 C.F.R. § 1.141(b).

5.2 For purposes of complying with the requirements of 37 C.F.R. § 1.143, Applicants provisionally elect Group 15 in the event restriction requirement becomes final. Applicants understand that such election is for search purposes only, and as required under this section to fully respond to the office letter (item number 9, page 8 of February 14, 2002 office letter), Applicants elect for restriction below in A-G, "specific" species of claim limitations found in the Group 15 generic independent claim 220 and claims 221-228 dependent thereon.

A) specific lipids	- elect 'phosphotidylcholine' as found in claim 221.
B) specific MHC component	- elect 'an α1 and β subunit set of a Class II MHC' as found in claim 226.
C) specific antigens	- elect 'dnaJp1' as disclosed on page 43, line 28, and page 72, lines 15-16 of the specification.
D) specific accessory molecules	- elect 'LFA-1' as found in claim 227.

E) specific orienting molecules - elect 'GM-1/cholera toxin β subunit' as disclosed, for example, at page 15, lines 14-15, page 22, lines 4-11, page 42 lines 8-9, and Example 18, the molecules being used together. For search purposes the Examiner may desire to search either individually but preferably together.

F) specific surfactant molecules - elect 'cholesterol' found in claim 222.

G) specific labels - elect 'fluorochrome'.

5.3 The Examiner will appreciate that all claims readable on claim 220 (*i.e.*, claims that include all the limitations of this claim) directed to an aAPC comprising liposome components, MHC components, antigen components, accessory molecule components and molecules for orienting molecules of interest are:

I) Composition claims 229-367 by virtue of the fact that each of the independent claims drawn to aAPCs (*i.e.*, claims 246, 273, 300, 328, 342) and necessarily their respective dependent claims each comprise these core elements.

II) Kit claims 198-210 by virtue of the fact that claim 198 comprises as elements liposome components (*i.e.*, lipids, neutral phospholipids, phosphotidylcholine), MHC components, antigen components, and accessory molecules.

III) Method claims 162-175 by virtue of the fact that each of the independent claims thereof (*i.e.*, claims 162, 163, 168) comprise aAPC prepared according to independent composition claims 220, 246, 273, 300, 328, 342 and necessarily named claims dependent thereon (*i.e.*, claims 222, 223, 228, 232, 233, 236, 248, 249, 255, 262, 275, 276, 282, 286, 287, 289, 303, 310, 314, 315, 317, 341, 344, 350, 354, and 357). Additionally, claims 195 and 196 because they use the method of claim 162, and claims 176-185, 186-188, 189-194, and 218 because they use the method of claim 163.

All claims readable on dependent claim 221 (*i.e.*, claims that include all the limitations of this claim) directed to an aAPC comprising liposome components, MHC components, antigen components, accessory molecule components and molecules for orienting molecules of interest wherein the liposome component comprises a lipid selected from a phospholipid, a neutral phospholipid, and phosphotidylchholine are:

I) Composition claims 222-228, 231-245, 247-255, 258-272, 274-282, 285-299, 301-310, 313-327, 329-341, 343-350, and 353-367 by virtue of the fact that claims 222, 231, 247, 258, 274, 258, 274, 285, 301, 313, 329, 343, 353 and each of their respective dependent claims include each of the above listed elements.

II) Kit claims 198-210 by virtue of the fact that claim 198 comprises as elements lipids, neutral phospholipids, phosphotidylcholine, MHC components, antigen components, and accessory molecule components.

III) Method claims 162, 163 and 168 by virtue of the fact that these claims include as elements aAPC prepared according to composition claims 222, 223, 228, 232, 233, 236, 248, 249, 255, 262, 275, 276, 282, 286, 287, 289, 302, 303, 310, 314, 315, 317, 341, 344, 350, 354, and 357. Additionally, claims 195 and 196 because they use the method of claim 162, and claims 176-185, 186-188, 189-194, and 218 because they use the method of claim 163.

Claims readable on dependent claim 222 (*i.e.*, claims that include all the limitations of this claim) directed to an aAPC comprising liposome components, MHC components, antigen components, accessory molecule components, molecules for orienting molecules of interest, and a surfactant component wherein said surfactant is cholesterol in contact with at least the liposome components, and wherein the liposome component comprises a lipid selected from a phospholipid, a neutral phospholipid, and phosphotidylchholine are:

I) Composition claims 223-228, 232-245, 248-255, 259-272, 275-282, 286-299, 302-310, 314-327, 329-341, 344-350, and 354-367 by virtue of the fact that each of these claims includes these core elements.

II) Kit claims 198-210 by virtue of the fact that claim 198 comprises as elements lipids, neutral phospholipids, phosphotidylcholine, cholesterol, MHC components, antigen components, and accessory molecules.

III) Method claims 162, 163 and 168 by virtue of the fact that these claims include as elements aAPC prepared according to composition claims 222, 223, 228, 232, 233, 236, 248, 249, 255, 262, 275, 276, 282, 286, 287, 289, 302, 303, 310, 314, 315, 317, 341, 344, 350, 354, and 357. Additionally, claims 195 and 196 because they use the method of claim 162, and claims 176-185, 186-188, 189-194, and 218 because they use the method of claim 163.

Claims readable on dependent claim 225 (*i.e.*, claims that include all the limitations of this claim) directed to an aAPC comprising liposome components, MHC components, antigen components, accessory molecule components, molecules for orienting molecules of interest, and a surfactant component wherein said surfactant is cholesterol in contact with at least the liposome components, and wherein the liposome component comprises a lipid selected from a phospholipid, a neutral phospholipid, and phosphotidylchholine, and wherein the antigen component is selected from a peptide, a peptide derived from a recipient for graft versus host diseases, a cancer cell-derived peptide, a peptide derived from an allergen, a donor-derived peptide, a pathogen-derived molecule, a peptide derived by epitope mapping, a self-derived molecule, a self-derived molecule that has sequence identity with said pathogen-derived antigen, said sequence identity having a range selected from the group consisting of between 5 and 100%, 15 and 100%, 35 and 100%, and 50 and 100% are:

I) Composition claims 237, 251, 264, 278, 291, 305, 319, 332, 347, and 359 by virtue of the fact that each of these claims includes these core elements.

II) Kit claims 198-210 by virtue of the fact that claim 198 comprises elements lipids, neutral phospholipids, phosphotidylcholine, cholesterol, MHC components, antigen components, and accessory molecule components.

III) Method claims 162, 163 and 168 by virtue of the fact that these claims include as elements aAPC prepared according to composition claims 222, 223, 228, 232, 233, 236, 248, 249, 255, 262, 275, 276, 282, 286, 287, 289, 302, 303, 310, 314, 315, 317, 341, 344, 350, 354, and 357 although the specific species of the antigen in these claims is not specified. Additionally, claims 195 and 196 because they use the method of claim 162, and claims 176-185, 186-188, 189-194, and 218 because they use the method of claim 163.

Claims readable on dependent claim 226 (*i.e.*, claims that include all the limitations of this claim) directed to an aAPC comprising liposome components, MHC components, antigen components, accessory molecule components, molecules for orienting molecules of interest, and a surfactant component wherein said surfactant is cholesterol in contact with at least the liposome components, and wherein the liposome component comprises a lipid selected from a phospholipid, a neutral phospholipid, and phosphotidylchholine, and wherein the MHC components is selected from a natural MHC, a recombinant MHC having sufficient composition

for binding an antigen, an α1 and α2 subunit set of a Class I MHC, an α1 and β subunit set of a Class II MHC, a peptide derived from said α and β subuits, and a portion of a natural MHC having sufficient composition for binding an antigen, are:

I) Composition claims 238, 252, 265, 279, 292, 306, 320, 333, 348, and 360 by virtue of the fact that each of these claims include the above core elements.

II) Kit claims 198-210 by virtue of the fact that claim 198 comprises elements lipids, neutral phospholipids, phosphotidylcholine, cholesterol, full length MHC components (*i.e.*, natural MHC) or portions thereof sufficient to bind an antigen, antigen components, and accessory molecules.

III) Method claims 162, 163 and 168 by virtue of the fact that these claims include as elements aAPC prepared according to composition claims 222, 223, 228, 232, 233, 236, 248, 249, 255, 262, 275, 276, 282, 286, 287, 289, 302, 303, 310, 314, 315, 317, 341, 344, 350, 354, and 357. Additionally, claims 195 and 196 because they use the method of claim 162, and claims 176-185, 186-188, 189-194, and 218 because they use the method of claim 163.

Claims readable on dependent claim 227 (*i.e.*, claims that include all the limitations of this claim) directed to an aAPC comprising liposome components, MHC components, antigen components, accessory molecule components, molecules for orienting molecules of interest, and a surfactant component wherein said surfactant is cholesterol in contact with at least the liposome components, and wherein the liposome component comprises a lipid selected from a phospholipid, a neutral phospholipid, and phosphotidylchholine, and wherein the accessory molecule components are selected from LFA-1, CD11a/18, CD54(ICAM-1), CD106(VCAM), CD49d/29(VLA-4), and antibodies to ligands of the foregoing molecules, are:

I) Composition claims 239, 253, 266, 280, 293, 307, 321, 334, 349, and 361 by virtue of the fact that each of these claims include the above core elements.

II) Kit claims 198-210 by virtue of the fact that claim 198 comprises elements lipids, neutral phospholipids, phosphotidylcholine, cholesterol, MHC components, antigen components, and accessory molecules.

III) Method claims 162, 163 and 168 by virtue of the fact that these claims include as elements aAPC prepared according to composition claims 222, 223, 228, 232, 233, 236, 248, 249, 255, 262, 275, 276, 282, 286, 287, 289, 302, 303, 310, 314, 315, 317, 341, 344, 350, 354,

and 357 although the specific species of the accessory molecule in these claims is not specified. Additionally, claims 195 and 196 because they use the method of claim 162, and claims 176-185, 186-188, 189-194, and 218 because they use the method of claim 163.

Claims readable on dependent claim 228 (*i.e.*, claims that include all the limitations of this claim) directed to an aAPC comprising liposome components, MHC components, antigen components, accessory molecule components, molecules for orienting molecules of interest, and a surfactant component wherein said surfactant is cholesterol in contact with at least the liposome components, and wherein the liposome component comprises a lipid selected from a phospholipid, a neutral phospholipid, and phosphotidylchholine, and wherein the molecules for orienting are selected from GM-1, a pentasaccharide, a ganglioside, and cholera toxin β subunit, are:

I) Composition claims 235-236, 255, 262-263, 282, 289-290, 310, 317-318, 341, 350, 357-358 by virtue of the fact that each of these claims include the above core elements.

II) Kit claim 381 by virtue of the fact that the claim comprises elements lipids, neutral phospholipids, phosphotidylcholine, cholesterol, MHC components, antigen components, accessory molecules, and molecules for orienting molecules of interest.

III) Method claims 162, 163 and 168 by virtue of the fact that these claims include as elements aAPC prepared according to composition claims 222, 223, 228, 232, 233, 236, 248, 249, 255, 262, 275, 276, 282, 286, 287, 289, 302, 303, 310, 314, 315, 317, 341, 344, 350, 354, and 357 although the specific species of the orientation molecule in claims 222, 223, 232, 233, 248, 249, 275, 276, 286, 287, 302, 303, 314, 315, 344, and 354 is not specified. Additionally, claims 195 and 196 because they use the method of claim 162, and claims 176-185, 186-188, 189-194, and 218 because they use the method of claim 163.

5.4 In the event the restriction is vacated, in whole or in part, to further the expedited prosecution of the application, Applicants further elect below in H-K for search purposes the following specific claim element species:

H) a specific co-stimulatory molecule - elect 'B7-1' as found in claim 240.

I) a specific adhesion molecule - elect 'anti-LFA-1' as found in claim 242.

J) a specific cell modulation molecule - elect 'anti-cytokine receptor' as found in claim 241.

K) a specific irrelevant molecule - elect 'streptavidin' as disclosed at page 34, lines 21-22, page 45, lines 17-18, and page 69, line 6.

6. Arguments for traversal of restriction requirement and for supporting Petition to the Commissioner to review the requirement.

Although Applicants appreciate the efforts of the Examiner, it is clear that the Examiner has failed to understand the nature of the claimed invention. This misunderstanding has apparently resulted in the Examiner improperly dicing the inventor's conception into dozens of perceived independent and distinct inventions. Applicants appreciate that the Examiner is not required to present all possible divisions, however, in making such divisions, even if they were proper, the Examiner has made numerous errors respecting the claims. Specifically, in Group 24 claims 246-247 are not directed to aAPC comprising among other elements, an adhesion molecule. In Group 27, claims 246-247 are not directed to aAPC comprising among other elements, a surfactant and an adhesion molecule. In Group 28, claims 246-247 are not directed to aAPC comprising among other elements, a surfactant and a cell modulation molecule and claims 256-258 are not directed to include a surfactant. In Group 29, claims 246-247 are not directed to aAPC comprising among other elements, a surfactant and an irrelevant molecule and claims 256-258 are not directed to inclusion of a surfactant. In Group 30, claims 273-274 are not directed to aAPC comprising among other elements, an adhesion molecule. Because of this error Group 30 is identical to Group 31. Therefore, Group 31 is superfluous. In Group 32, claims 273-274 are not directed to aAPC comprising among other elements, an irrelevant molecule. In Group 43, claims 342-342 are not directed to aAPC comprising among other elements, a co-stimulatory molecule. In Group 44, claims 342-342 are not directed to aAPC comprising among other elements, an adhesion molecule. In Group 45, claims 342-342 are not directed to aAPC comprising among other elements, a cell modulation molecule. In Group 46, claims 342-342 and 351-353 are not directed to aAPC comprising among other elements, a surfactant. In Group 50 the Examiner has referred to claims 342-361 and 366-367 as being directed to aAPC comprising among other elements, irrelevant molecules. Applicants are puzzled as to why claim 365, directed to an irrelevant molecule and to which claims 366-367 are dependent, was not included.

Likewise for Group 51, claims 369-380 were referenced but not the independent claim 368 from which claims 369-380 depend. In Group 3 the Examiner states that claims 162-167 are drawn to a method of "characterizing" T cells. However, claim 162 is directed to "identifying" T cells, claim 163 is directed to "isolating" T cells, claim 164 is directed to a further step in claim 163 of quantifying T cells, and claim 166 refers to sources for T cells. Only claim 165 invokes "characterizing" specifically the "functional phenotype of T cells" and amended claim 167 depends now on claim 165. Thus, Group 3 as stated is incorrect since only claim 165 (which includes all the limitations of claims163 and 164) falls into the stated invention category.

6.2 In dividing the claims apparently based on the Markush groups of claims 229, 256, 283, 311, and 351, the Examiner appears to take the position that distinct inventions may be based on only one element of the group at a time. However, Applicants respectfully note that the claims state ". . .further comprising molecular components selected from the group . . ." (*i.e.*, plural components). Thus, as claimed, these claims may be read covering use of any one, combination of any of, or all of the listed members of the group taken together. Under the Examiner's restriction organization, not just singular additional components could be added to the base claims but dozens of combinations would be required to fully describe the embodiments of the invention further requiring literally hundreds of restrictions. Clearly, hundreds of independent and distinct inventions is not what the Applicant intends. Rather, as clearly discussed throughout the specification, there is described a unified invention comprising artificial APC comprising various preferred embodiments or elements that provide the APC with various characteristics. With respect to restriction of Markush-type claims where the members of the Markush group are sufficiently few in number and so closely related that a search and examination of the entire claim can be made without *serious* burden, the Examiner *must* examine all the members of the Markush group (MPEP 803.02). With respect to the aAPC composition of matter claims, Applicants respectfully note that each and every group into which the Examiner has divided the claims (*i.e.*, Groups 14-50) as well as Method claim Group 51 are searchable within the same Class and subclass (*i.e.*, Class 435 subclass 325). Thus, the Examiner has restricted, in an enormous number of ways, members of Markush groups having only 5 or fewer members (*i.e.*, Markush groups of claims 229, 256, 283, 311, 351) wherein the members are very closely related in the context of their art recognized immunological application. Given that the 37 Groups

fabricated by the Examiner are all to be found in a single Class and subclass, not only will the Examiner necessarily search all of the elements simultaneously, such a common search can not as a practical matter comprise any serious burden.

6.3 Further, other of the Method claim Groups (*i.e.*, Groups 1, 2, 3, 6, 7, 11, 12, and 13) are admitted by the Examiner to be searchable in the same Class 435 as the above discussed composition of matter claims. Moreover, of these, Groups 1, 2, 3, 7, 12, and 13 are all searchable under Class 435 with Group 12 searchable in the same subclass 325 and Groups 1, 2, 3, 7, 12, and 13 searchable in the same subgroup 7.1. Still further, Groups 6 and 11 are searchable in a single subgroup 6. Thus, with respect to the above discussed Groups, only a **single Class and three subclasses** are required for searching a great majority of the claims.

Given the simplicity of such effort so required, the Examiner states that Groups 2 and 3 would require searching additionally only in Class 424, subclasses 278.1 and 534. Favorably, Groups 4 and 5 are stated to be searchable in the same Class 424 and subclasses. Thus, **a total of only two Classes and five subclasses are required** for searching all the claims of the application other than claims 196 (Group 8), 215 (Group 10), and 197-214 (Group 9). Remarkably, the simplicity of searching is further apparent even for these last three Groups because they are **all found in the same two Classes** (*i.e.*, 435 and 424) stated above and only three additional subclasses (*i.e.*, subclass 184.1, 283.1, and 810, respectively). Thus, remarkably, ***all 219 claims are searchable under only two Classes and eight subclasses.***

6.4 As detailed in the MPEP section 803.02, the spirit of the law underlying restriction practice of Markush-type claims centers on the relatedness of the group members and under *In re Weber* 580 F.2d 455 (CCPA 1978) it is improper for the Office to refuse to examine that which the Applicant regards as his invention unless the subject matter in a claim lacks unity of invention. Under *In re Harnish* 631 F.2d 716 (CCPA 1980) and *Ex parte Hozumi* 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984) such unity exists where compounds within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility. By analogy to these holdings, the present claims are unified by their common core features (*i.e.*, aAPC comprising liposome components, MHC components, antigen components, accessory molecule components, and molecules for orienting molecules of interest). The unity is

further found with respect to the members of the Markush group (*i.e.*, costimulatory, adhesion, cell modulation, irrelevant and label molecules) by the nature of their common application in the aAPC of participating together in the modulation/education of T cell responses. Collectively, such components provide their respective essential contributions in the various disclosed embodiments engineered into the aAPC to achieve the desired T cell manipulation. As clearly laid out in the Guidelines referred to in MPEP 803, for there to be plural inventions supportive of a restriction requirement, both of the following criteria must be demonstrated; (A) the inventions must be independent or distinct, AND (B) there must be a serious burden on the Examiner. As Applicants have laid out above, the second of these requirements has not been demonstrated. Further, as discussed below, the first of these criteria are also not met.

6.5 With respect to the independence and distinctness of inventions, the general principles laid out in the MPEP 806 state that where inventions are independent (*i.e.*, **no disclosed relation therebetween**), restriction is ordinarily proper. However, where inventions are related as disclosed but are not distinct as claimed, restriction is **never** proper. Further, as clearly set forth in MPEP 806.03, where claims of an application define the same essential characteristics of a single disclosed embodiment of an invention, restriction should never be required. "This is because the claims are but different definitions of the same disclosed subject matter, varying in breadth or scope of definition." (MPEP 806.03)

The instant invention fits this very situation which can easily be recognized by the fact that all of the claims are linked by the same single disclosed and claimed core embodiment, *i.e.* aAPC comprising liposome components, MHC components, antigen components, accessory molecule components, and molecules for orienting molecules of interest. From this core set of elements, claims dependent thereon which add additional elements as well as independent claims and their respective dependent claims comprising such additional elements in varying combinations "are but different definitions of the same disclosed subject matter, varying in breadth or scope of definition."

Section 806.04 of the MPEP further defines independence of inventions such that, for example, two different combinations, "not disclosed as capable of use together," . . . are independent. The example refers to a shoe vs a locomotive bearing. In the instant invention, all of the elements (*i.e.*, molecules that can be used in an aAPC) are disclosed as capable of use

together and are not unrelated as indicated by the spirit of the MPEP's example. Rather, they are related in the context of their immunologic utility as disclosed in detail in the specification and claimed. The second example of this section of the MPEP suggests that where two inventions are process and apparatus wherein the apparatus "cannot be used to practice the process or any part thereof," they are independent. In contrast, the apparatus of the present invention, as claimed in the "column" claim (claim 215), can be used to practice the process, *i.e.*, (method) claims directed to modulation of T cells. Therefore, as to these inventions restriction should not be required.

MPEP section 808.01 provides yet further clarification as to what is "independent." Specifically, "where [the inventions] are **not connected in design, operation, or effect** under the disclosure of the particular application under consideration (MPEP 806.04), the facts relied on for this conclusion are in essence the reasons for insisting upon restriction." In the instant case the aAPC in their various embodiments (which the Examiner in error restricted) are without question "connected in design, operation, [and] effect," in that the aAPC are the base design used in the operation of interactions with T cells to bring about the effect of modulating T cells. As a practical matter the aAPC are also "connected" to their method of making, use, and utility in connection with the column apparatus.

6.6 The Examiner appears to have premised his restriction on the basis of "distinctness" of the claimed combinations (paragraph 4, page 7 of the office letter). Applicants respectfully direct the Examiner's attention to MPEP 806.05(c) which states, "In order to establish that combination and subcombination inventions are distinct, two-way distinctness must be demonstrated" and "reasons" why insisting on restriction is necessary. The necessity example invokes as such reason "separate classification, status, or field of search." Applicants respectfully point out above that there are only two Classes and between three, five, and eight subclasses that the Examiner has identified to cover all 219 claims and only one Class and subclass with respect to the aAPC composition and process of making claims. Thus, restriction on the basis of necessity does not appear reasonable.

Inventions meet the showing of two-way distinctness if the claimed combination (A) does not require the particulars of the subcombinations as claimed for patentability, AND (B) the subcombination can be shown to have utility either by itself or in other and different relations.

MPEP 806.05(c) provides under example II that where the relationship between the claims is such that the separately claimed subcombination constitutes the essential distinguishing feature of the combination the inventions are not distinct. In the instant case, for example, the aAPC claim 220 comprises five elements which can be viewed as a subcombination that constitutes the essential feature of any of the other combination of elements as claimed in the aAPC composition of matter claims 229, 246, 256, 273, 283, 300, 311, 328, 342, and 351.

For completeness of argument, although Applicant's respectfully maintain that the aAPC composition claims as constructed include only a single claimed subcombination, it could be argued that the claims as constructed include two or more claimed subcombinations (*e.g.* claim 246 being a subcombination of claim 229). However, such an analysis would, under MPEP 806.05(d), require analysis of whether the several subcombinations are generically claimed. As further stated in that section, where subcombinations as disclosed and claimed are both (a) species under a claimed genus and (b) related, restriction must be determined by both the practice of election of species and the practice applicable to related inventions. "If restriction is improper under either practice, it should not be required (MPEP 806.04(b)." As discussed above, Applicants believe that the inventions are related and therefore on this basis alone restriction should not be required.

6.7 With respect to whether hypothetical subcombinations are species under a claimed genus, the issue of whether the subcombinations are generically claimed is raised. As discussed in MPEP 806.04(d), generally, a generic claim should include no material element additional to those recited in the species claims and must comprehend within its confines the organization covered in each of the species. Further, for purposes of obtaining claims to more than one species, the generic claims cannot include limitations not present in each of the species claims. Applicants respectfully note that the various aAPC composition independent claims 246, 273, 300, 328, and 342 not only are combinations that include the related subcombination of claim 220, they comprise generic claims that do not include limitations not present in species claims that can be devised out of dependent claims that possess Markush groups. Given that the Examiner has identified the plurality of the claims as generic (page 9 of the office letter), Applicants respectfully submit that notwithstanding the apparent difficulty in divining whether the application includes generic claims that do not include limitations not present in species

claims given the lack of specific species claims, a careful examination of the claims will reveal that due to the chain of dependency of the claims, and the relatedness of the various combinations, the claims do indeed meet the definition of generic claims. This further raises the issue discussed in 809.02 (d) *i.e.*, that where only generic claims are present, no restriction can be required except in applications where the generic claims recite such a multiplicity of species that an unduly extensive and burdensome search is necessary.

As discussed above respecting burden on the Examiner for searches, there are only Two Classes and between 3, 5 and 8 subclasses required for a complete search. Applicants respectfully note that since all of the aAPC composition claims include the core elements of a liposome component, and MHC component, an antigen component, an accessory molecule component and an orienting molecule component, *i.e.*, a mere 5 components, and given that examples of each of these components (for all the claim sets) are provided in claims 221, 225-228 a search for these combinations will fulfill the searching needs for a majority of the components of all of the aAPC composition claims. Necessarily, if members of this grouping by a search of the individual species combinations is found allowable, all of the generic aAPC independent claims should be allowable. Further, if the added element of a surfactant and a label pursuant to claims 222 and 224 are included, the patentability of most of the claims would be easily determined. The Examiner has already effectively authorized such a search by creating restriction Group 15.

Further, if a search pursuant to determining the patentability of Group 15 has been determined by the Examiner as not comprising an undue burden, then searching the additional elements of costimulatory, adhesion, cell modulation, and irrelevant molecules (all under the same Class as already searched for Group 15 should also not comprise any undue burden.

6.8 MPEP 809.02 discusses the linking of species under generic claims pursuant to 37 C.F.R. 1.146 such that a reasonable number of species may be claimed in the same application. Applicants maintain that notwithstanding the complex construction of the claims, there are a reasonable number of species to consider. Particularly, there are only 6 preferred generic constructs of aAPC indicated by claims 220, 246, 273, 300, 328, and 342. Claim 328 represents a construct wherein all of the above named molecular elements are in a single independent claim. This same construct would be found in each of claims 232, 259, 286, 314, and 354 if all of the

members of the Markush groups of claims 229, 256, 283, 311, and 351 were used. Thus, a search for one claim set would necessarily locate appropriate results for the others. Given the limited number of species in addition to those already required under Group 15, there should be no material burden on the Examiner to conduct such search.

7. Particular issues raised in the Office action and further reasons for withdrawal of restriction.

In paragraphs 4-7 of the Office action, the Examiner proposes various arguments for supporting a restriction requirement of the claims.

7.1 In paragraph 4, the Examiner bases restriction on the premise that the "kit" and "column" claims (*i.e.*, claims 197-214 and new claim 381, and claim 215, respectively) are distinct from aAPC composition claims (*i.e.*, claims 220-367) under the view that they are distinct "products" having various component combinations. Applicants respectfully traverse this assessment and request reconsideration. As discussed above, the aAPCs, which are claimed as elements of the kits and the column, comprise various elements that are related under criteria spelled out in the MPEP.

Further, Applicants respectfully submit that the kit, column and aAPCs are not fairly distinguishable simply as products, but comprise process and apparatus for its practice as outlined in MPEP section 806.05(e). This section states that process as claimed (here process of practicing T cell *manipulation* according to the various method claims) and apparatus for its practice (here a kit and/or column as claimed) can be shown to be distinct if either or both (**A**) the process as claimed (in the present case method claim 162 directed to method of identifying T cells specific for and antigen, method claims 163-167 directed to method of isolating T cells specific for an antigen, method claims 168-175 directed to method of modulating T cell response, method claims 176-185 directed to method of characterizing the functional state of antigen-specific T cells, method claims 186-194 directed to method of treating a condition, method claim 195 directed to identifying antigen-specific T cells using the method of claim 162, and claim 196 directed to a method of treating a mammal to reduce rejection of allografts using aAPC) can be practiced by another materially different apparatus or by hand, or (**B**) that the apparatus as claimed (claims 197-213 and 381 directed to a kit comprising aAPC and/or immunomodulatory column, and claim 215 directed to an immunomodulatory column) can be

used to practice another or materially different process. Moreover, if the apparatus claims include a claim to "means" for practicing the process, the claim is a linking claim and must be examined with the elected invention. Also, if it is ultimately allowed, rejoinder is required. (MPEP 809.04)

With respect to the above paragraph, the Examiner has not complied with his burden of showing either A or B. Applicants (A) know of no known *process as claimed* that can be practiced by another materially different apparatus as there is no apparatus, other than the kits and column described in the present specification, disclosed for using as an integral element aAPC. Moreover, Applicants submit that the *apparatuses as claimed* are not designed to practice a different process, material or not.

In any event, the kit apparatus claims include a claim for practicing the process (*i.e.*, claim 205) and the column apparatus claims also include a claim for practicing the process (*i.e.*, new claim 382). Thus, even if these claims are restricted they must be rejoined when the aAPC composition claims are found allowable.

7.2 In paragraph 5 of the office action the Examiner characterizes method of making aAPC (claims 368-380) and the a APC composition claims (220-367) as being related with respect to a process of making and product made. Applicants agree with this assessment. However, Applicants respectfully traverse the Examiner's assessment of distinction between the groups of claims and request its reconsideration. According to MPEP 806.05(f), distinction is present between a product made a process of its making if either or both (A) the process as claimed is not an obvious process of making the product and the process as claimed can be used to make other and different products, or (B) that the product as claimed can be made by another and *materially* different process. In the first instance, the Examiner has not presented any reasonable examples of obviousness of the process and its use in making other products. Applicants submit that since no other products than the disclosed aAPC are possible, there is no argument that can be presented to support distinctness based on the criteria of (A). Second, the Examiner has presented the argument (based on criteria (B)) that distinction is to be had because "the product as claimed can be made by adding the antigen after the incorporation of the MHC complex." If the Examiner is contending that the timing of addition of an antigen in the process of making

aAPC is *material* to the process, Applicants respectfully submit that the Examiner's supposition is entirely incorrect.

Although the process claim 368 appears to read on use of a preformed MHC:antigen complex, use of such a complex is purely a preferred embodiment over a less preferred addition of MHC and antigen separately. Applicants direct the Examiner's attention to page 60, lines 5-19 of the specification which clearly discusses that one embodiment of the present inventive process is the separate addition of MHC and antigen into the liposome. Specifically, "Complexes of affinity-purified MHC molecules . . . were inserted into liposomes . . . The [antigen peptides] were incubated with the liposome:MHC complexes . . . to form liposome:MHC:b-peptide complexes." This excerpt is found in Example I under Materials and Methods. Further, Applicants respectfully direct the Examiner's attention to page 102 lines 17-30 found under Methods of Example 17 where it is stated "After preincubation of [labeled] peptides and MHC at conditions based on *in vitro* MHC binding, MHC-peptide complexes were added to the [liposomes]." Thus, as clearly laid out in the specification, the process of making the product comprises an interchangeable (*i.e.*, distinctly immaterial) step of adding the components. Therefore, the Examiner has not met his burden of showing a *material* distinction between the process of making and product made.

7.3 In paragraph 6 of the office action the Examiner characterizes the kit, column, aAPC, and methods of use as being related products and processes of use. Applicants agree with this assessment in part but respectfully submit that the assessment is incomplete. Specifically, the methods of making the aAPC should also be considered related to the products and processes of use and be judged with respect to restriction practice under criteria laid out in MPEP section 806.05(i). Further, since the Examiner has surmised a distinction between the products and processes of use, and Applicants disagree with such assessment, Applicants respectfully traverse the Examiner's finding and request reconsideration.

Under 37 C.F.R. 1.141, where claims to all three categories, product, process of making, and process of use, are included in a national application, a three way requirement for restriction can only be made where the process of making is distinct from the product. If the process of making and the product are not distinct, the process of using may be joined with the claims

directed to the product and the process of making the product even though a showing of distinctness between the product and process of using the product can be made.

As noted under MPEP 806.05(i), distinctness is identified as outlined in MPEP 806.05(f) and rests upon the *materiality* of difference between processes that can be identified in making the product. Applicants have specifically pointed out above that no such materiality exists respecting the Examiner's example. Therefore, upon finding allowability of the product claims (*i.e.* the aAPC, kit, and/or column) the process of using must not be restricted unless distinctness can be shown between the process of using and the product according to MPEP 806.05(h). However, since 37 C.F.R. 1.141 specifically provides that where there is no distinctness between the process of making and product made, the process of using must be joined, and no such distinction has been set forth by the Examiner in the instant case, the product, process of its making, and process of use must be examined in the present application.

For completion of argument, Applicants respectfully point out that MPEP 806.05(h) provides that distinction between a product and process of using can be shown (A) if the process of using *as claimed* can be practiced with another *materially* different product, or (B) the product *as claimed* can be used in a *materially* different process. Applicants submit that neither of these circumstances can be shown. With respect to (A), each of the processes of use (*i.e.*, claims 162, 163-167, 168-175, 176-185, 186-188, 189-194, 195, 196, and 218) all require as elements use of aAPC as claimed in this application. Thus, the process of using as claimed specifically requires use of the aAPC product, not another product materially different or otherwise. With respect to (B), the aAPC product as disclosed and claimed is designed in its various embodiments to be used for T cell manipulation which, as the use claims indicate, harbor numerous T cell related uses. The Examiner posits that the product can be used to produce antibodies. This concept is not accurate. The aAPC of the present invention are designed to affect T cells. T cells do not produce antibodies, rather B cells produce antibodies. Therefore, the Examiner's assertion is not correct and he has not met his burden of showing distinctness between the product and process of using the product.

7.4 In paragraph 7 of the office letter the Examiner characterizes the various process of use claims as being patentably distinct based on their employment of different steps to achieve

different products or information. As discussed above in 7.3, the process of use claims must be retained where there is no material distinction between the product and process of use.

Importantly, Applicants respectfully bring to the Examiner's attention that the great majority of the claims in the present application are linking claims as described under MPEP 809.03. Specifically, restriction is prevented between inventions where there is: (A) genus claims that link species claims; (B) a claim to necessary process of making a product (*e.g.*, aAPC) is linked to the product; (C) a claim to a means for practicing a process (*e.g.*, kit or column apparatus) links apparatus and process claims; and (D) a claim to the product linking the process of making and using. Applicants submit that all of these circumstances are present in the present application. However, of the presently pending claims, Applicants submit that only claims 216-217 and 219 are not properly linked to avoid restriction.

8. Since the claims of the above proposed groups I-IV are linked, an initial examination of groups I and II will provide the basis for inclusion of the claims of groups III and IV upon the generic claims of group I being found allowable.

9. Given the invention of the present application relates to cancer Applicants further submit with this response a Petition to Make Special under 37 C.F.R. 1.102(d) and fee (§ 1.17(h)) for the early allowance of claims.

10. Since this case concerns complex subject matter, an early in-person interview may be deemed appropriate. I will be in Washington, D.C. July 29-31, 2002 and will be available for discussions.

11. No fee other than the fee required for petitions and extension of time is believe due respecting the instant response, however, if any fee not covered is due, please charge our deposit account Number 50/1273 in the appropriate amount. If the If the Examiner needs to reach me, my direct telephone number is (858) 720-2757.

Respectfully submitted,
Brobeck, Phleger & Harrison LLP

Dated: 4/15/02

By: _____
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Version with marking to show changes made and clean copy of replacement and new claims.

In the claims the following amendments are made.

162. (Amended) A method of identifying T cells specific for an antigen of interest comprising:

(b) obtaining a biological sample containing T cells which are specific for an antigen of interest;

(c) preparing an artificial antigen presenting cell comprising attributes of any of the claims selected from the group consisting of [claim 1, claim 3, claim 4, claim 11, claim 13, claim 14, claim 17, claim 27, claim 29, claim 30, claim 38, claim 40, claim 44, claim 54, claim 56, claim 57, claim 65, claim 67, claim 68, claim 71, claim 81, claim 83, claim 84, claim 93, claim 95, claim 96, claim 99] claim 220, claim 222, claim 223, claim 228, claim 232, claim 233, claim 236, claim 246, claim 248, claim 249, claim 255, claim 262, claim 273, claim 275, claim 276, claim 282, claim 286, claim 287, claim 289, claim 300, claim 302, claim 303, claim 310, claim 314, claim 315, claim 317, claim 328, claim 341, claim 342, claim 344, claim 350, claim 354, claim 357, wherein the antigen in said artificial antigen presenting cell is said antigen of interest;

(d) contacting the biological sample obtained in step (a) with the artificial antigen presenting cell obtained in step (b) to form an artificial antigen presenting cell:T cell complex; wherein at least one element of said artificial antigen presenting cell is associated with a label, said elements selected from the group consisting of said antigen of interest, an irrelevant molecule, a lipid layer, a lipid, an MHC molecule components, a co-stimulatory components, an adherent components, a cell modulation components, and an accessory molecule components; and

detecting said label.

163. (Amended) A method of isolating T cells specific for an antigen of interest comprising:

(a) obtaining a biological sample containing T cells which are specific for an antigen of interest;

(b) preparing an artificial antigen presenting cell comprising attributes of any of the claims selected from the group consisting of [claim 1, claim 3, claim 4, claim 11, claim 13, claim 14, claim 17, claim 27, claim 29, claim 30, claim 38, claim 40, claim 44, claim 54, claim 56, claim 57, claim 65, claim 67, claim 68, claim 71, claim 81, claim 83, claim 84, claim 93, claim 95, claim 96, claim 99] claim 220, claim 222, claim 223, claim 228, claim 232, claim 233, claim 236, claim 246, claim 248, claim 249, claim 255, claim 262, claim 273, claim 275, claim 276, claim 282, claim 286, claim 287, claim 289, claim 300, claim 302, claim 303, claim 310, claim 314, claim 315, claim 317, claim 328, claim 341, claim 342, claim 344, claim 350, claim 354, claim 357, wherein the antigen in said artificial antigen presenting cell is said antigen of interest;

(c) contacting the biological sample obtained in step (a) with the artificial antigen presenting cell obtained in step (b) to form an artificial antigen presenting cell:T cell complex; wherein at least one element of said artificial antigen presenting cell is associated with a label, said elements selected from the group consisting of said antigen of interest, an irrelevant molecule, a lipid layer, a lipid, an MHC molecule components, a co-stimulatory components, an adherent components, a cell modulation components, and an accessory molecule components;

(d) removing said artificial antigen presenting cell:T cell complex formed in step (c) from said biological sample; and

(e) separating T cells specific for said antigen of interest from said artificial antigen presenting cell:T cell complex.

167. (Amended) A method according to claim [166] 165 wherein said biological sample is selected from the group consisting of whole blood, blood cells, blood plasma, and tissue.

168. (Amended) A method of modulating T cell response comprising:

(a) isolating T cells which are specific for an antigen of interest using a method of claim 163; and

(b) contacting said isolated T cells with an artificial antigen presenting cell comprising attributes of any of the claims selected from the group consisting of [claim 1, claim 3,

claim 4, claim 11, claim 13, claim 14, claim 17, claim 27, claim 29, claim 31, claim 38, claim 40, claim 44, claim 54, claim 56, claim 57, claim 65, claim 67, claim 68, claim 71, claim 81, claim 84, claim 93, claim 95, claim 96, claim 99] claim 220, claim 222, claim 223, claim 228, claim 232, claim 233, claim 236, claim 246, claim 248, claim 249, claim 255, claim 262, claim 273, claim 275, claim 276, claim 282, claim 286, claim 287, claim 289, claim 300, claim 302, claim 303, claim 310, claim 314, claim 315, claim 317, claim 328, claim 341, claim 342, claim 344, claim 350, claim 354, claim 357, wherein said antigen presenting cell has an antigen of interest or a homologue of said antigen of interest, said artificial antigen presenting cell further having at least on molecule selected from the group consisting of an accessory molecule components, a co-stimulatory components, an adhesion components, and a cell modulation components.

176. (Amended) A method of characterizing the functional state of antigen-specific T cells comprising:

[(e)] (a) isolating T cells in accordance with the method of claim 163;

[(f)] (b) extracting mRNA from said isolated T cells;

[(g)] (c) obtaining cDNA corresponding to said extracted mRNA;

[(h)] (d) evaluating the mRNA encoding proteins that govern function and phenotype of said antigen-specific T cells, said evaluation carried out by a method selected from the group consisting of (1) mRNA translation of said proteins and testing said proteins using antibodies against such proteins, and (2) rtPCR of the mRNA using primers specific for said proteins.

Clean copy of amended claims.

162. (Amended) A method of identifying T cells specific for an antigen of interest comprising:

(a) obtaining a biological sample containing T cells which are specific for an antigen of interest;

(b) preparing an artificial antigen presenting cell comprising attributes of any of the claims selected from the group consisting of claim 220, claim 222, claim 223, claim 228, claim 232, claim 233, claim 236, claim 246, claim 248, claim 249, claim 255, claim 262, claim 273, claim 275, claim 276, claim 282, claim 286, claim 287, claim 289, claim 300, claim 302, claim 303, claim 310, claim 314, claim 315, claim 317, claim 328, claim 341, claim 342, claim 344, claim 350, claim 354, claim 357, wherein the antigen in said artificial antigen presenting cell is said antigen of interest;

(c) contacting the biological sample obtained in step (a) with the artificial antigen presenting cell obtained in step (b) to form an artificial antigen presenting cell:T cell complex; wherein at least one element of said artificial antigen presenting cell is associated with a label, said elements selected from the group consisting of said antigen of interest, an irrelevant molecule, a lipid layer, a lipid, an MHC molecule components, a co-stimulatory components, an adherent components, a cell modulation components, and an accessory molecule components; and

(d) detecting said label.

163. (Amended) A method of isolating T cells specific for an antigen of interest comprising:

(a) obtaining a biological sample containing T cells which are specific for an antigen of interest;

(b) preparing an artificial antigen presenting cell comprising attributes of any of the claims selected from the group consisting of claim 220, claim 222, claim 223, claim 228, claim 232, claim 233, claim 236, claim 246, claim 248, claim 249, claim 255, claim 262, claim 273, claim 275, claim 276, claim 282, claim 286, claim 287, claim 289, claim 300, claim 302, claim 303, claim 310, claim 314, claim 315, claim 317, claim 328, claim 341, claim 342, claim 344,

claim 350, claim 354, claim 357, wherein the antigen in said artificial antigen presenting cell is said antigen of interest;

(c) contacting the biological sample obtained in step (a) with the artificial antigen presenting cell obtained in step (b) to form an artificial antigen presenting cell:T cell complex; wherein at least one element of said artificial antigen presenting cell is associated with a label, said elements selected from the group consisting of said antigen of interest, an irrelevant molecule, a lipid layer, a lipid, an MHC molecule components, a co-stimulatory components, an adherent components, a cell modulation components, and an accessory molecule components;

(d) removing said artificial antigen presenting cell:T cell complex formed in step (c) from said biological sample; and

(e) separating T cells specific for said antigen of interest from said artificial antigen presenting cell:T cell complex.

167. (Amended) A method according to claim 165 wherein said biological sample is selected from the group consisting of whole blood, blood cells, blood plasma, and tissue.

168. (Amended) A method of modulating T cell response comprising:

(c) isolating T cells which are specific for an antigen of interest using a method of claim 163; and

(d) contacting said isolated T cells with an artificial antigen presenting cell comprising attributes of any of the claims selected from the group consisting of claim 220, claim 222, claim 223, claim 228, claim 232, claim 233, claim 236, claim 246, claim 248, claim 249, claim 255, claim 262, claim 273, claim 275, claim 276, claim 282, claim 286, claim 287, claim 289, claim 300, claim 302, claim 303, claim 310, claim 314, claim 315, claim 317, claim 328, claim 341, claim 342, claim 344, claim 350, claim 354, claim 357, wherein said antigen presenting cell has an antigen of interest or a homologue of said antigen of interest, said artificial antigen presenting cell further having at least on molecule selected from the group consisting of an accessory molecule components, a co-stimulatory components, an adhesion components, and a cell modulation components.

176. (Amended) A method of characterizing the functional state of antigen-specific T cells comprising:

(a) isolating T cells in accordance with the method of claim 163;

(b) extracting mRNA from said isolated T cells;

(c) obtaining cDNA corresponding to said extracted mRNA;

(d) evaluating the mRNA encoding proteins that govern function and phenotype of said antigen-specific T cells, said evaluation carried out by a method selected from the group consisting of (1) mRNA translation of said proteins and testing said proteins using antibodies against such proteins, and (2) rtPCR of the mRNA using primers specific for said proteins.

381. (New) A kit according to claim 198 wherein said artificial APCs have the further component of molecules for orienting molecules of interest selected from the group consisting of GM-1, a pentasaccharide, a ganglioside, and cholera toxin β subunit.

382. (New) An immunomodulatory column according to claim 215 wherein said column is used for a process of manipulating T cell populations, said process selected from the group consisting of identifying T cells specific for an antigen of interest according to claim 162, isolating T cells specific for an antigen of interset according to claim 163, modulating T cell response according to claim 168, characterizing the functional state of antigen-specific T cells according to claim 176, treating a condition in a subject which would be benefited by altering the functional pattern of cytokine production by certain antigen-specific T cells according to claim 186, treating a condition in a subject which would be benefited by increasing Th-1 response according to claim 189, identifying antigen-specific T cells specific for epitopes on a graft donor's tissue according to claim 195, and treating a recipient mammal to reduce rejection of allografts in a transplantation therapy regimen according to claim 196.